mmoles) in 50 ml. of anhydrous pyridine was set up exactly as described for the analogous adenosine reaction. After 2 days at room temperature the solvent was evaporated, and the residue was applied in water to a 4 × 25 cm. column of DEAE cellulose (HCO_3^-). After a water wash the products were eluted with a linear gradient of 8 l. of triethylammonium bicarbonate (0.005 to 0.25 *M*). Five peaks were obtained as follows: peak I (21%) was unreacted TMP-morpholidate; peak II (10%) was mainly dithymidine pyrophosphate plus a little TMP; peak III (26%) was mainly TP_3T plus a little TDP; peak IV (26%) was mainly TP_4T plus some TTP; peak V (15%) was TP_5T and TP_4.

(a) **P^1,P^3-Di(thymidine-5′)triphosphate (TP_3T).**—Peak III (4900 optical density units at 267 mμ) was evaporated to dryness and freed from excess bicarbonate by evaporation with methanol. The material was dissolved in water, adjusted to pH 7 with ammonia, and applied to a 2 × 25 cm. column of DEAE cellulose (acetate). Elution with a linear gradient of 2 l. of ammonium acetate (pH 5.0, 0.005 to 0.30 *M*) cleanly separated TTP (13%) from TP_3T (87%). The latter peak was diluted fourfold with water and adjusted to pH 7.7 with ammonium hydroxide. It was then passed through a column containing 50 ml. of DEAE cellulose (HCO_3^-) and washed thoroughly with water. The product was then quantitatively eluted with 0.5 *M* triethylammonium bicarbonate, evaporated to dryness, and isolated in the usual way as the hydrated calcium salt (131 mg.) which was chromatographically homogeneous in several solvents: R_f in solvent A, 0.20; in solvent B, 0.20.

TP_3T requires that total P-labile P-thymidine = 1.50:0.50:1.00. Found: total P-labile P-thymidine = 1.58:0.53:1.00. The ammonium salt of TP_3T (0.5 μmole) remained completely unchanged upon incubation with 50 μl. of *E. coli* alkaline phosphatase and released only 1.6% of its total phosphorus as orthophosphate by this treatment. The action of venom phosphodiesterase-I (50 μl.) and Tris buffer, pH 9 (5 μl.), on 0.5 μmole of TP_3T resulted in complete conversion to TMP and TDP within 15 min., the latter compound being only slowly hydrolyzed to TMP and orthophosphate.

(b) **P^1,P^4-Di(thymidine-5′)tetraphosphate (TP_4T).**—The majority of peak IV (4100 optical density units) was purified on a 3 × 20 cm. column of DEAE cellulose (acetate) using a linear gradient of 2 l. of ammonium acetate, pH 5 (0.005 to 0.5 *M*) giving 38% TTP and 62% TP_4T. The latter compound was desalted and isolated as its calcium salt (130 mg.) by the same methods used for TP_3T.

TP_4T requires that total P-labile P-thymidine = 2.00:1.00:1.00. Found: total P-labile P-thymidine = 2.01:0.86:1.00. The product was chromatographically homogeneous and had R_f 0.15 in solvent A and 0.14 in solvent B. Incubation with 50 μl. of *E. coli* alkaline phosphatase produced no new ultraviolet-absorbing products but did release 4.8% of the total phosphorus as orthophosphate. Venom phosphodiesterase (10 μl.) converted TP_4T into equimolar amounts of TMP and TTP within 30 min. and gave only TMP and pyrophosphate after overnight incubation.

Conformational and Configurational Studies on Some Acetylated Aldopyranosyl Halides[1,2]

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A series of poly-*O*-acetylated aldopyranosyl halide derivatives (I–X), each in the thermodynamically more stable anomeric form, has been studied by n.m.r. spectroscopy. The halides examined included derivatives of all four pentoses, three hexoses (glucose, galactose, and mannose), and three derivatives of 2-amino-2-deoxyglucose. All compounds studied were of the D series. Comparison spectra of α-D-lyxose tetraacetate and β-D-mannose pentaacetate were obtained. In deuteriochloroform solution, the signal of the anomeric (C-1) proton is observed at lower field than the signals of the other ring protons. Analysis of the spectra of the halides reveals that the stable anomer in every case has the halogen atom axial when the molecule concerned is in its favored conformation. All of the halides studied exhibited a high degree of conformational purity in solution. The n.m.r. data confirm anomeric configurational assignments previously based solely upon optical rotatory data. The stable form of tri-*O*-acetyl-D-lyxopyranosyl bromide (known only as a sirup) is shown to be the α-D anomer in the *C1* conformation.

The poly-*O*-acetylaldopyranosyl halides theoretically can exist in either of two anomeric forms, differing in configuration at C-1, and both forms have been prepared in several instances.[3] The configurations assigned to these derivatives are based on optical rotatory data through application of Hudson rules of rotation,[4] and are supported by mechanistic data[5] on the reactions they undergo. In the case of the poly-*O*-acetylaldopyranosyl halides of those simple sugars where both anomeric forms are known, there can be little reasonable doubt as to the correctness of these assignments, although direct proof by methods such as X-ray crystallographic analysis is lacking. When only one anomeric form is known, configurational assignment on the basis of optical rotation may be more difficult. When one of the acetoxy groups is replaced by a different substituent, as in the *O*-acetylated glycosyl halides of amino sugars,[6] further problems in configurational assignment may be introduced, since it has been noted[7,8] that certain substituent groups at C-2 may cause a complete reversal of normal rotatory relationships between anomers.

Poly-*O*-acetylaldopyranosyl halides readily undergo anomeric interconversion[5] in the acetic acid–hydrogen halide and similar mixtures commonly used to introduce the halogen atom at C-1. The major product of the equilibrated reaction is consequently the thermodynamically more stable anomer.

Rules have been formulated,[3] based on configurational relationships of the ring substituents, for predicting

(1) Supported in part by Grant-in-Aid No. 19187 from The Ohio State University Development Fund, and in part by the Agricultural Research Service, U. S. Department of Agriculture, Grant No. 12-14-100-7208(71) (The Ohio State University Research Foundation Project 1827), administered by the Northern Regional Research and Development Division, Peoria, Ill.

(2) Preliminary reports of part of this work have been given: (a) Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p. 1D; (b) *Chem. Commun.* (London), 113 (1965).

(3) For reviews, see (a) L. J. Haynes and F. H. Newth, *Advan. Carbohydrate Chem.*, **10**, 207 (1955); (b) J. Staněk, M. Černý, J. Kocourek, and J. Pacák, "The Monosaccharides," Academic Press Inc., New York, N. Y., 1963, pp. 198–220.

(4) C. S. Hudson, *J. Am. Chem. Soc.*, **31**, 66 (1909).

(5) R. U. Lemieux, *Advan. Carbohydrate Chem.*, **9**, 1 (1954).

(6) See D. Horton in "The Amino Sugars," R. W. Jeanloz and E. A. Balasz, Ed., Academic Press Inc., New York, N. Y., 1965, in press, for a discussion of glycosyl halide derivatives of amino sugars.

(7) Y. Wang and H.-I. Tai, *Acta Chim. Sinica*, **24**, 368 (1958).

(8) D. Horton, *J. Org. Chem.*, **29**, 1776 (1964).

CHART I

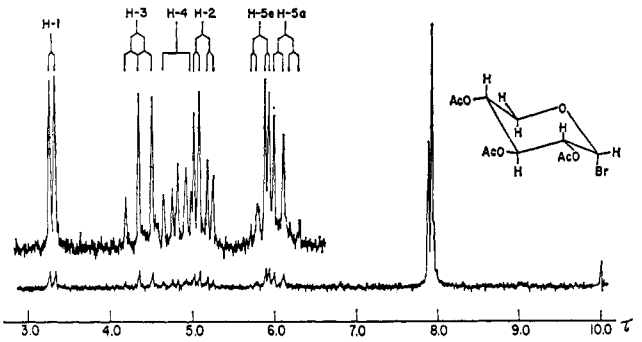


Figure 1.—The n.m.r. spectrum of tri-*O*-acetyl-α-D-xylopyranosyl bromide (I) at 60 Mc.p.s. in deuteriochloroform.

the anomeric configuration of the more stable anomer of a poly-*O*-acetylaldopyranosyl halide. Conformational arguments based on unfavorable steric interactions between axial halogen and other axial ring substituents have been advanced[9] to explain the anomeric preference, and have been discussed.[5] The more stable anomeric form of the poly-*O*-acetylaldopyranosyl halides of the common aldohexoses is α (D or L) in each case, and, since the favored ring conformation will be that having the minimum number of instability factors[10] such as axial ring substituents, it is clear that the halogen atom will be axial in the favored ring conformation. This preference for a halogen atom (or other polar group) at C-1 to adopt the axial orientation, as a thermodynamically more stable arrangement than the equatorial orientation, contrary to the usual order of conformational stabilities predicted from steric considerations, has been termed the anomeric effect.[11,12] It has been explained[13] in terms of an unfavorable parallel interaction between an equatorial C-1–halogen dipole and the atomic dipole formed by the resultant of the unshared p electrons on the ring oxygen atom. The generality of this model has been amply verified[11,12,14]; the effect resembles the behavior of 2-halocyclohexanones, where the axial orientation of the halogen atom is also favored.[15] To what extent the anomeric effect may compete with steric and other interactions in determining the favored anomeric configuration and ring conformation of poly-*O*-acetylaldopyranosyl halides is, however, not always clear.

The present work reports an analysis of the n.m.r. spectra of 10 poly-*O*-acetylaldopyranosyl halides, each in the thermodynamically more stable anomeric form. The study includes the four pentose configurations, three hexose configurations, and three derivatives of 2-amino-2-deoxy-D-glucose.

Materials and Methods

Each compound studied was prepared under conditions involving equilibration in an acetic acid–hydrogen bromide mixture, or in an acetyl halide medium. These systems give the thermodynamically more stable anomeric form in each case. The tri-*O*-acetyl-D-pentopyranosyl bromides with the α-D-*xylo*, β-D-*arabino*, and β-D-*ribo* configurations, the tetra-*O*-acetyl-D-hexopyranosyl bromides with the α-D-*gluco* and α-D-*galacto* configurations, and 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride, 3,4,-6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide, and 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide, were all obtained in crystalline form, and had physical constants in good agreement with the literature values (see Experimental Section). Tetra-*O*-acetyl-D-mannopyranosyl bromide was obtained as a sirup from 1,2,3,4,6-penta-*O*-acetyl-β-D-mannopyranose and ethereal hydrogen bromide. Tri-*O*-acetyl-D-lyxopyranosyl bromide,[16] which has not been obtained crystalline, was prepared by treatment of crystalline 1,2,3,4-tetra-*O*-acetyl-α-D-lyxopyranose with hydrogen bromide in acetic acid.

The n.m.r. spectra were measured at 60 Mc.p.s. on the freshly prepared compounds in deuteriochloroform, with tetramethylsilane as the internal standard. Spectra were analyzed on a first-order basis,[17] and the recorded coupling constants are the directly observed line spacings. It is recognized that the observed spacings may be smaller than the absolute J values owing to second-order effects,[18] and the recorded J values may be regarded as minimum values of the absolute coupling constants $|J|$.

Spectral data for the ten compounds are tabulated in Tables I–III, and further details are included in the Experimental Section. The tables also list n.m.r. data for 1,2,3,4-tetra-*O*-acetyl-α-D-lyxopyranose and 1,2,3,4,6-penta-*O*-acetyl-β-D-mannopyranose as reference compounds.

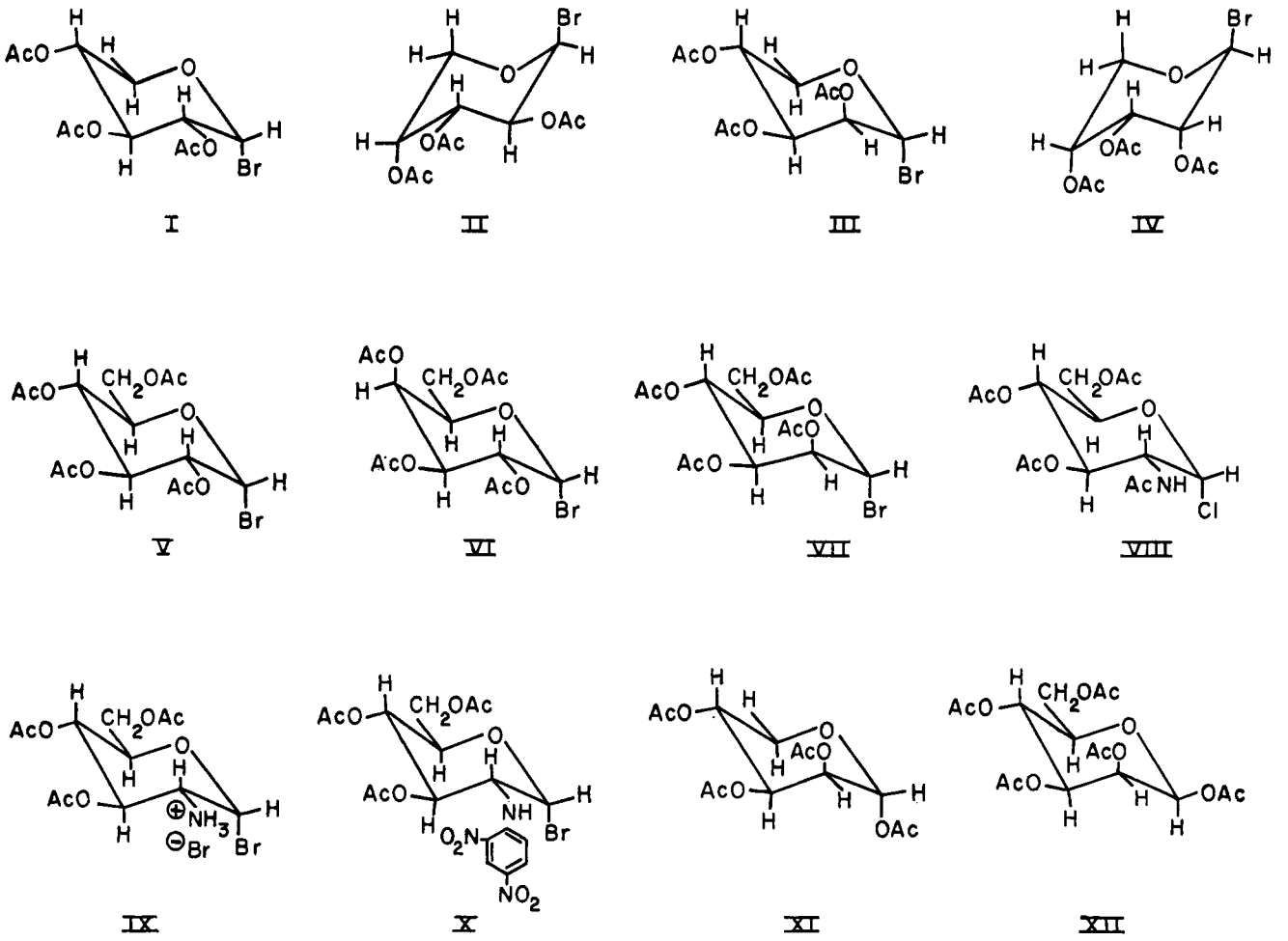
Results and Discussion

Analysis of the spectra indicate that all 10 poly-*O*-acetylated aldopyranosyl halides exist preponderantly in the respective chairlike conformations (I–X) shown (Chart I). The data are in agreement with the anomeric assignments made to each compound on the basis of optical rotatory values. The sirupy tri-*O*-acetyl-D-lyxopyranosyl bromide of Levene and Wolfrom[16] is shown to be preponderantly the α-D anomer in the *C1* conformation.

Tri-*O*-acetyl-α-D-xylopyranosyl Bromide.—The n.m.r. spectrum (Figure 1) of this compound is well resolved and permits a complete first-order analysis, which is fully consistent with formulation of the compound as I, the α-D anomer in the *C1* conformation. In common with all of the compounds studied in this series, the C-1 proton signal appears at lower field than the other ring proton signals, because of the combined deshielding effects of the halogen atom and the ring

(9) O. Hassel and B. Ottar, *Acta Chem. Scand.*, **1**, 929 (1947).
(10) R. E. Reeves, *Advan. Carbohydrate Chem.*, **6**, 107 (1951).
(11) R. U. Lemieux in "Molecular Rearrangements," part 2, P. de Mayo, Ed., Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1964, pp. 735–743.
(12) S. J. Angyal in "Conformational Analysis," E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, Ed., Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1965, Chapter 6.
(13) J. T. Edward, *Chem. Ind.* (London), 1102 (1955).
(14) C. Altona, C. Romers, and E. Havinga, *Tetrahedron Letters*, **No. 10**, 16 (1959).
(15) J. Allinger and N. L. Allinger, *Tetrahedron*, **2**, 64 (1958).
(16) P. A. Levene and M. L. Wolfrom, *J. Biol. Chem.*, **78**, 525 (1928).
(17) Chemical shift values are given on the τ scale, and correspond to the midpoint of each singlet or symmetrical multipet. For unsymmetrical multiplets the chemical shifts were calculated as weighted mean values. In those cases where a signal formed part of a complex multiplet, or where satellite peaks were difficult to observe, the chemical shifts and observed line splittings are given as approximate (~) values.
(18) R. U. Lemieux and J. W. Lown, *Can. J. Chem.*, **41**, 889 (1963)

CHART I



oxygen. This H-1 signal in I appears at τ 3.30 as a doublet ($J_{1,2}$ = 4.0 c.p.s.) indicating[19-21] a projected angle between the C-1 and C-2 carbon–hydrogen bonds (1,2 projected valence angle) of approximately 60°. The H-2 signal appears at relatively high field, τ 5.13, as a quartet through coupling with H-1 and also with H-3. The large value of the $J_{2,3}$ coupling constant (10 c.p.s.) indicates the *trans*-diaxial arrangement of H-2 and H-3. The H-3 signal appears at relatively low field, τ 4.35, attributable to the deshielding effect of the bromine atom in the *syn*-diaxial relation with H-3. A similar deshielding has been observed[22] in the case of the 9α proton in 12α-bromo-5α-androstan-11-one. The H-3 signal in I is observed as a triplet with a large spacing (10 c.p.s.) between the lines, due to equal coupling with axial protons at C-2 and C-4. The H-4 signal appears at higher field, τ 4.84, as a multiplet, the X portion of an ABXY system,[23] due to coupling of H-4 with the protons on C-5 (AB portion) and on C-3 (Y portion). The total width of this multiplet (20 c.p.s.) is approximately equal to the sum of the first-order coupling constants $J_{3,4} + J_{4,5a} + J_{4,5e}$, and the splitting between the principal outer lines and the center line of the multiplet is 10 c.p.s., equal to $J_{3,4}$. The C-5 proton signals form an eight-line pattern with the appearance typical of the AB portion of an ABX system, and the two protons show a geminal coupling of 11.4 c.p.s. The quartet at τ 5.86 was assigned to the equatorial proton on C-5 since it shows small coupling with H-4 ($J_{4,5e}$ = 2.6 c.p.s.), indicating a 4,5e projected valence angle of about 60°. The higher field quartet, at τ 6.11, was assigned to the axial proton at C-5, since the large first-order coupling with H-4 ($J_{4,5a}$ = 6.9 c.p.s.) indicates a *trans*-diaxial relation with H-4.

All of these data fully support the structure I depicted, and are inconsistent with any other anomeric or conformational assignment. The signals for the three acetoxy groups fall within the range expected[19,21,24] for equatorial secondary acetoxy groups.

Tri-*O*-acetyl-β-D-arabinopyranosyl Bromide.—The n.m.r. spectrum of this compound (Figure 2) is fully consistent with the β-D configuration in the *1C* conformation as shown (II), and excludes the opposite α-D configuration or alternate chair conformation.

(19) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **79**, 1005 (1957).

(20) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Am. Chem. Soc.*, **85**, 2870 (1963).

(21) L. D. Hall, *Advan. Carbohydrate Chem.*, **19**, 51 (1964).

(22) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p. 75.

(23) For details of the ABX notation and analysis of spin-coupled systems, see (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959; (b) J. D. Roberts, "An Introduction to Spin-Spin Splitting in High-Resolution Nuclear Magnetic Resonance Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962; (c) F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961).

(24) J. C. Sowden, C. H. Bowers, L. Hough, and S. H. Shute, *Chem. Ind.* (London), 1827 (1962); L. D. Hall and L. Hough, *Proc. Chem. Soc.*, 382 (1962); L. D. Hall, L. Hough, K. A. McLauchlan, and K. Pachler, *Chem. Ind.* (London), 1465 (1962); L. D. Hall, L. Hough, S. H. Shute, and T. J. Taylor, *J. Chem. Soc.*, 1154 (1965).

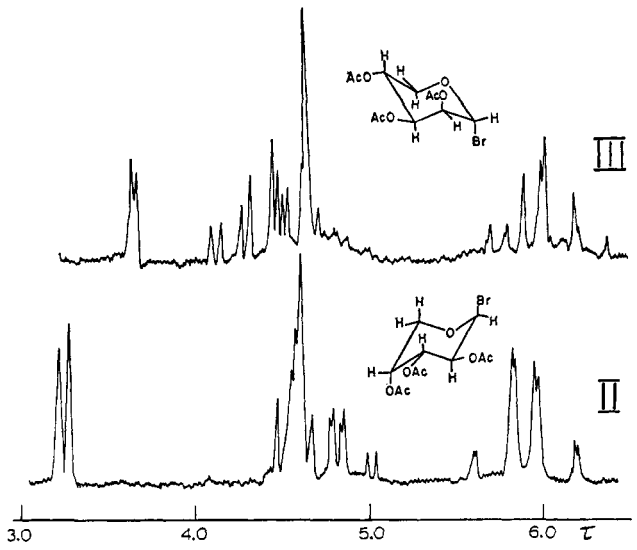


Figure 2.—The low-field portions of the n.m.r. spectra of tri-*O*-acetyl-β-D-arabinopyranosyl bromide (II) and tri-*O*-acetyl-α-D-lyxopyranosyl bromide (III), at 60 Mc.p.s. in deuteriochloroform.

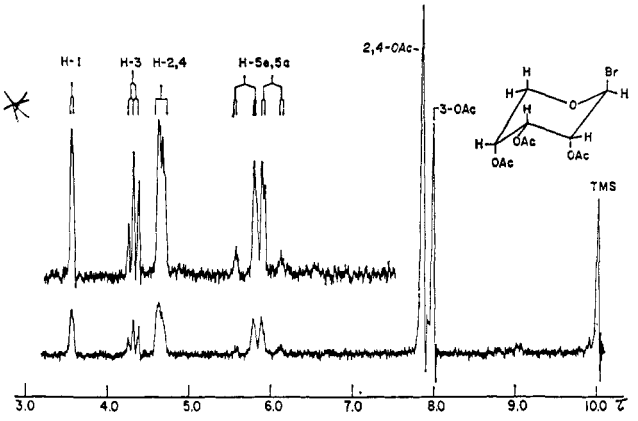


Figure 3.—The n.m.r. spectrum of tri-*O*-acetyl-β-D-ribopyranosyl bromide (IV) at 60 Mc.p.s. in deuteriochloroform.

The narrow doublet at lowest field, τ 3.25, assigned to H-1, indicates a 1,2 projected valence angle of about 60°. Two partially overlapping quartets are observed at τ 4.89 and 4.71, whose line spacings indicate that each proton is axial and is flanked by one axial and one equatorial proton. The lower field quartet, τ 4.71 was assigned to H-3, deshielded[22] by the *syn*-axial bromine atom, and the τ 4.89 quartet was assigned to H-2. This assignment is supported by the slightly different $J_{1,2}$ and $J_{3,4}$ first-order couplings observable in an expanded spectrum. The H-4 signal is observed as a narrow multiplet centered at τ 4.52, and the spacing of the principal outer lines is observed to be $J_{3,4} + J_{4,5a} + J_{4,5e}$. The C-5 protons form the AB portion of an ABX system and show geminal coupling of the usual order, but the first-order $J_{4,5e}$ and $J_{4,5a}$ couplings are small (1–2 c.p.s.), indicating that the H-4 bond, viewed along the C-4–C-5 axis, bisects the angle of the two H-5 bonds. This supports the *1C* conformation shown (II) and excludes the *C1* conformation, which would have 4,5 diaxial protons and would thus give a $J_{4,5a}$ coupling constant of larger magnitude. The small splitting of the H-1 signal therefore verifies the β-D configuration.

The acetoxy group signals provide further, independent verification of structure II, since one signal is observed at relatively low field (τ 7.86) in the region indicative[19,21,24] of the axial orientation (4-OAc), and the other two signals are observed at higher field, indicative of the equatorial orientation (2,3-OAc). The low-field position of the H-4 signal may be ascribed to the equatorial orientation of H-4.

Tri-*O*-acetyl-α-D-lyxopyranosyl Bromide.—This compound was obtained as a sirup, $[\alpha]_D$ +95° (chloroform), and analysis of the n.m.r. spectrum (Figure 2) indicates that it is almost entirely the α-D anomer in the *C1* conformation as formulated (III). Included in the tables for comparison are n.m.r. data for 1,2,3,4-tetra-*O*-acetyl-α-D-lyxose (XI). The spectrum of III shows a low-field doublet, τ 3.64, assigned to H-1, with $J_{1,2}$ = 1.8 c.p.s. The quartets at τ 4.19 and 4.48 can be assigned to H-3 and H-2, respectively. The H-2 signal is split into a narrow quartet by coupling with H-1 ($J_{1,2}$ = 1.8 c.p.s.) and with H-3 ($J_{2,3}$ = 3.2 c.p.s.). The H-3 signal shows the small $J_{2,3}$ coupling, and a larger $J_{3,4}$ coupling (10.2 c.p.s.), indicating the *trans*-diaxial arrangement of H-3 and H-4. The H-5 protons form the AB portion of an ABX system, and the large value of the $J_{4,5a}$ first-order coupling (9.5 c.p.s.) indicates the *trans*-diaxial arrangement of H-4 and H-5a. One acetoxy proton signal is observed at relatively low field, τ 7.83, indicative[19,21,24] of the axial orientation, the other two acetoxy proton signals, at τ 7.90 and 7.95, fall in the range anticipated for equatorial acetoxy groups. All of these data provide firm support for the *C1* conformation. The deshielding effect of an axial bromine atom[22] on an axial proton at C-3 appears to be general, and the low-field location of the H-3 signal in III is thus strong indication that the bromine atom is axial and that III has the α-D configuration. The high, positive specific rotation observed is in good agreement with this.

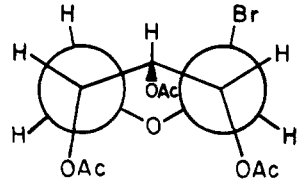
The n.m.r. spectrum of 1,2,3,4-tetra-*O*-acetyl-α-D-lyxopyranose showed features similar to that of III, but with an additional acetoxy group signal (1-OAc) in the region indicative of an axial acetoxy group. The appearance of a low-field narrow doublet for H-1 (τ 4.06, $J_{1,2}$ = 3.0 c.p.s.), and the values of the $J_{4,5e}$ and $J_{4,5a}$ first-order couplings indicate that the *C1* conformation (XI) is the preponderant form,[25] as predicted from consideration of the anomeric effect.[11,12] The H-2, H-3, and H-4 signals were incompletely resolved, but it is noteworthy that the H-3 signal occurs at much higher field in XI than it does in III, where strong deshielding by axial bromine is proposed.

Tri-*O*-acetyl-β-D-ribopyranosyl Bromide.—The n.m.r. spectrum for this compound (Figure 3) fully supports formulation as the β-D anomer in the *1C* conformation (IV), with the bromine atom and the acetoxy groups at C-2 and C-4 in the axial orientation, and only the C-3 acetoxy group oriented equatorially. The H-1 signal is observed at τ 3.57 as a narrow doublet, which excludes the possibility of a 1,2-*trans*-diaxial arrange-

(25) In this present work, a small proportion (<10%) of the unfavored conformer may escape detection. If conformational inversion is slow, the peaks of the unfavored conformer may be lost in the noise, while, if inversion is fast, the weighted means of the coupling parameters for the two conformers would differ little from those of the preponderant conformer alone. See S. Brownstein, *Can. J. Chem.*, **40**, 870 (1962); R. J. Abraham and W. A. Thomas, *J. Chem. Soc.*, 335 (1965).

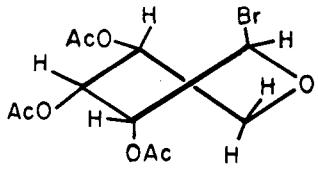
ment of protons. The C-2, -3, and -4 proton signals are observed as a two-proton multiplet at τ 4.67 and a one-proton triplet at τ 4.33. The lower field triplet was assigned to H-3, oriented axially and *syn* to axial bromine at C-1, and split into a narrow triplet by equal coupling with the equatorial protons on C-2 and C-4. The two-proton multiplet at τ 4.67 is assigned to H-2 and H-4; the band is relatively narrow (~10 c.p.s.) since all vicinal coupling constants are small. The C-5 proton signals appear at τ 5.68 and 6.01, as the AB portion of an ABX system, and show normal geminal coupling. The values of $J_{4,5a}$ and $J_{4,5e}$ are both small, as in the case of the D-*arabino* analog II, and verify the *1C* conformation for IV, since the alternate conformation would have given a large $J_{4,5a}$ first-order coupling. The *1C* conformation is further supported by the positions of the acetoxy group signals. Two of these are observed at relatively low field, τ 7.85, indicative[19,21,24] of the axial orientation (2,4-OAc); the third signal, τ 7.98, appears in the region indicating the equatorial orientation (3-OAc).

Steric repulsion of axial groups may cause some flattening of the ring in IV, to give a distorted chair as depicted in XIII. The consequent recession of H-1

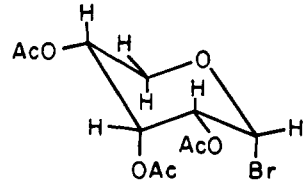


XIII

and H-2 to a projected angle greater than the true *gauche* (60°) relationship would predictably[20,21] give a small value for $J_{1,2}$. A conformation in the flexible cycle, for example, XIV, is not considered probable since any reasonable model which allows for the anomeric effect[11,12] would give one approximately *trans*-diaxial $J_{4,5}$ coupling.



XIV



XV

The general appearance of the spectrum of IV showed little change when the sample was cooled to −40°. Any of the alternate *C1* conformer which may have been present was in too small a proportion to detect by the methods used.[25]

The β-D anomer is the more stable form of tri-*O*-acetyl-D-ribopyranosyl bromide, notwithstanding the fact that it has two axial acetoxy groups in the favored *1C* conformation, while the α-D anomer, depicted in the *C1* conformation (XV) would have only one axial acetoxy group, at C-3. It is therefore apparent that an axial acetoxy group on the same side of the ring as an axial bromine atom is a destabilizing factor of greater magnitude than two axial acetoxy groups on the other side of the ring.

Tetra-*O*-acetyl-α-D-hexopyranosyl Bromides.—The derivatives with the D-*gluco*, D-*galacto*, and D-*manno* configurations gave n.m.r. spectra fully consistent with the assigned anomeric configurations in the *C1* conformation, as predicted on the basis of optical rotatory data[3,4] and Reeves conformational instability factors.[10] Analysis of the ring-proton signals for the three compounds revealed close similarities with the spectra of the pentose derivatives with the α-D-*xylo*, β-D-*arabino*, and α-D-*lyxo* configurations, respectively.

The low-field portion of the spectrum of tetra-*O*-acetyl-α-D-glucopyranosyl bromide is shown in Figure 4. Similarities between this spectrum and that of the homomorphous D-xylose analog (Figure 1) are clearly evident, and the spectrum is fully consistent with formulation as the α-D-glucose derivative in the *C1* conformation (V). The H-1 doublet appears at τ 3.38. The H-2 signal is clearly recognizable as a quartet, τ 5.18, showing axial–axial coupling with H-3 ($J_{2,3}$ = 10 c.p.s.) and axial–equatorial coupling with H-1 ($J_{1,2}$ = 4 c.p.s.); these assignments are in good agreement with data recently reported.[26] The H-3 and H-4 signals are observed as triplets with large first-order coupling constants (9.5–10 c.p.s.), since these protons are diaxially related and are flanked by axial protons at C-2 and C-5. The triplet at lower field, τ 4.42, may be assigned to H-3, since this proton can be deshielded[22] by the axial bromine atom. All of the acetoxy group signals are observed in the region characteristic[19,21,24] of equatorial and primary acetoxy groups.

Tetra-*O*-acetyl-α-D-galactopyranosyl bromide gave an n.m.r. spectrum consistent with the anticipated *C1* conformation (VI), and the small coupling of the H-1 signal (τ 3.23, $J_{1,2}$ = 3.5 c.p.s.) indicates the equatorial orientation of H-1. The H-2 and H-3 signals appear as quartets at τ 4.95 and 4.55, very close to the values observed for the β-D-arabinose derivative (II); the analysis of the signals is very similar and indicates a 2,3-*trans*-diaxial arrangement of protons, with coupling to the respective neighboring equatorial protons, at C-1 and C-4. The lower field signal (τ 4.55) was assigned to H-3, since this proton can experience deshielding from the axial bromine atom.[22] An incompletely resolved multiplet at τ 4.43 was assigned to the equatorial H-4. The lowest field acetoxy group signal in VI, at τ 7.86, is assigned[19,21,24] to the axial 4-acetoxy group. Structures VI and II are mirror-image homomorphs, and possess the same arrangement of axial and equatorial groups at C-1, -2, -3, and -4; the similarities of the proton resonance signals at these positions for the two derivatives are clearly evident.

The n.m.r. spectrum of tetra-*O*-acetyl-D-mannopyranosyl bromide is consistent with formulation as the α-D configuration in the *C1* conformation (VII), and it shows considerable similarity to that of the homomorphous pentose analog III having the α-D-*lyxo* configuration. The H-1 signal of VII appears as a narrow, but well-resolved doublet, τ 3.68 ($J_{1,2}$ = 1.6 c.p.s.). A quartet at τ 4.30 was assigned to H-3, and the first-order coupling constants ($J_{2,3}$ = 3 c.p.s., $J_{3,4}$ = 10 c.p.s.) indicate the 2,3-equatorial–axial and 3,4-diaxial arrangement of protons. The H-2 signal is

(26) R. U. Lemieux and D. R. Lineback, *Can. J. Chem.*, **43**, 94 (1965).

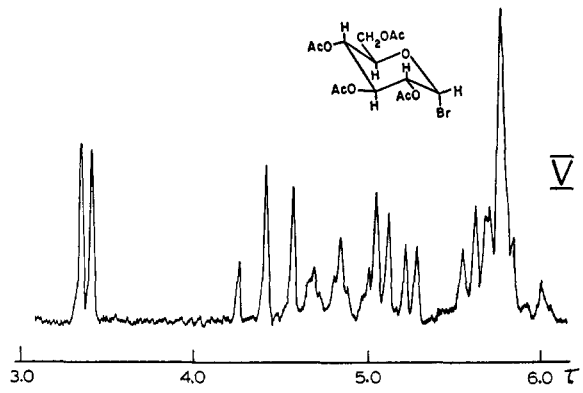


Figure 4.—The low-field portion of the n.m.r. spectrum of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (V) at 60 Mc.p.s. in deuteriochloroform.

observed at higher field, not fully resolved from the H-4 signal, as a narrow quartet since the $J_{1,2}$ and $J_{2,3}$ coupling constants are small and unequal. One acetoxy group signal appears at relatively low field, τ 7.83, and is assigned to the axial 2-acetoxy group.

1,2,3,4,6-Penta-*O*-acetyl-β-D-mannopyranose predictably[10] favors the *C1* conformation (XII), and comparison of the coupling parameters (see Table II) of XII and VII show close similarities. The H-2 and H-4 signals are observed at similar fields (see Table I) in both derivatives, but the H-3 signal is observed at τ 4.83 in XII, compared with τ 4.30 in VII, illustrating the strong deshielding[22] effect on H-3 of the *syn*-axial bromine atom in VII.

The small $J_{1,2}$ value observed for XII may be related to the fact that this compound possesses the Reeves Δ2 instability condition.[10] Comparative studies on related compounds are desirable, however, before rationalizations in terms of distortion of the chair conformation, or adjustments to the Karplus-type relationship, are attempted.

Conclusions Regarding the Acetylated Glycosyl Halides I–VII.—Comparison of the data for the seven derivatives I–VII indicates that the H-1 signal appears in the range τ 3.23–3.38 for the compounds (I, III, V, and VI) in which the C-2 acetoxy group is equatorial, whereas the H-1 signal appears at higher field (τ 3.57–3.68) for the compounds (III, IV, and VII) having an axial 2-acetoxy group. The latter group also give smaller values of the first-order $J_{1,2}$ coupling constant.

Steric repulsion of axial substituents in the second group (III, IV, and VII) may cause some flattening of the chairlike ring, although the possibility cannot be excluded that the Karplus-type relationship is affected[27] by the orientation of the electronegative 2-acetoxy group.

The favored conformation of each compound is that in which the bromine atom is axial, and the compounds appear to have a high degree of conformational purity[25] in solution. The observed conformations of I, II, and V–VII accord with those predicted[28] from considerations of steric interactions and the anomeric effect.

An axial proton at C-3 is deshielded by the *syn*-axial bromine atom at C-1. The axial H-3 signal appears at lower field than the H-2, -4, and -5 signals, except in the case where the acetoxy group at C-4 is axial. In the latter case, the H-3 signal appears at somewhat higher field, and the equatorial H-4 signal is observed at lower field. The axial bromine atom appears to deshield the *syn*-axial H-5a proton to some extent. Equatorial proton signals at H-2 and H-4 are observed at lower field than corresponding signals of axial protons.

2-Amino-2-deoxy-D-glucose Derivatives.—Three glycosyl halide derivatives of 2-amino-2-deoxy-D-glucose were included in the study. Each compound may be regarded as the thermodynamically more stable anomeric form, and the spectra are consistent with formulation of each derivative as the α-D anomer in the *C1* chair conformation, since the coupling parameters of the ring-proton signals showed close similarities with those of compounds I and V.

The n.m.r. spectrum of 2-acetamido-2-deoxy-α-D-glucopyranosyl chloride (VIII) showed a narrow doublet, τ 3.75, assigned to H-1, with $J_{1,2}$ = 3.5 c.p.s. A unit-proton doublet, τ 3.28 (J = 9 c.p.s.), was assigned to the NH proton, since it disappeared on deuteration without observed change of the rest of the spectrum, except in the region assigned to the H-2 signal. The observed splitting of the NH proton signal is due to coupling with H-2, and the broad appearance of the lines may be ascribed to nitrogen quadrupole coupling. The H-2 signal is complex owing to coupling with three different protons.

The H-1 signal of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide (IX) appears at very low field, τ 2.86, presumably on account of the extra inductive effect of the $-NH_3^+$ group. The proton signal of the latter function is observed at τ 1.38, as a broad three-proton multiplet through H–^{14}N coupling.

The small splitting of the H-1 signal in 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide has been given[8] as evidence for the assigned configuration, and consideration of further spectral parameters for this compound, listed in the tables, provide full support for this configuration in the *C1* conformation (X). The H-3 and H-4 triplets are well resolved; the H-2 signal is complex owing to coupling with the NH proton as well as with H-1 and H-3. A unit-proton doublet, τ 2.84 (J = 10 c.p.s.), was assigned to the NH proton. Aromatic proton signals in the region τ 0.9–1.8 can be analyzed in a manner previously described[8] for related 2,4-dinitroanilino derivatives (see Experimental Section).

The H-2 signals in VIII–X are observed at higher field than those of the 2-acetoxy analogs. The appearance of one of the acetoxy group signals in IX at relatively low field is probably due to the deshielding effect of the $-NH_3^+$ group.

In all of the foregoing it has been assumed that a small splitting of the H-1 signal in the poly-*O*-acetylglycosyl halides indicates a *gauche* relationship of H-1 and H-2, and excludes the *trans*-diaxial arrangement of protons. It is assumed that the halogen atom does not affect the approximate validity of the Karplus relationship. This is verified by the observation[29] that 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl

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TABLE I

CHEMICAL SHIFTS OF METHINE AND METHYLENE PROTONS

Compd.	Configuration	Chemical shifts,[a] τ H-1 e	H-2 e	H-2 a	H-3 a	H-4 e	H-4 a	H-5 e	H-5 a	H-6	H-6′
				Acetylated Aldopyranosyl Bromides							
I	α-D-*xylo*	3.30 d		5.13 q	4.35 t		4.84	5.86 q	6.11 q		
II	β-D-*arabino*	3.25 d		4.89 q	4.71 q	~4.52		<5.75 q,	6.05 q>		
III	α-D-*lyxo*	3.64 d	4.48 q		4.19 q		4.65	5.84 q	6.18 q		
IV	β-D-*ribo*	3.57 d	~4.67		4.33 t	~4.67		<5.72 q,	5.95 q>		
V	α-D-*gluco*	3.38[b] d		5.18 q	4.41 t		4.86 t		~5.72	5.71 q	5.84 q
VI	α-D-*galacto*	3.23 d		4.95 q	4.55 q	~4.43			5.48	5.78	5.88
VII	α-D-*manno*	3.68 d	4.57 q		4.30 q		4.67 t		~5.85	5.70 q	5.82 q
				Acetylated 2-Amino-2-deoxyaldopyranosyl Halides							
VIII[c]	α-D-*gluco*	3.75 d		5.48	4.58 t		4.80 t		~5.78	~5.73	~5.82
IX[d]	α-D-*gluco*	2.86 d		~5.52	4.61 t		~4.76		~5.95	~5.70	~5.70
X[e]	α-D-*gluco*	3.40 d		~5.50	4.38 t		4.69 t		~5.70	~5.65	~5.84
				Acetylated Aldopyranoses							
XI	α-D-*lyxo*	4.06 d	~4.78		~4.63 q		4.85	5.99 q	6.32 q		
XII	β-D-*manno*	4.09 d	4.50 q		4.83 q		4.67		6.18	5.68 q	5.84 q

[a] Observed multiplicities: d, doublet; t, triplet; q, quartet. In the case of complex, overlapping, or incompletely-resolved multiplets, the chemical shifts given may be approximate (~) values; e, equatorial; a, axial. [b] Supersedes the incorrect value given in ref. 2b. [c] *N*-Acetyl 1-chloride. [d] Hydrobromide 1-bromide. [e] *N*-(2,4-Dinitrophenyl) 1-bromide.

TABLE II

FIRST-ORDER COUPLING CONSTANTS OF METHINE AND METHYLENE PROTONS

Compd.	Configuration	Coupling constants,[a] c.p.s. $J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5e}$	$J_{4,5a}$	$J_{5a,5e}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
				Acetylated Aldopyranosyl Bromides						
I	α-D-*xylo*	4.0	10.0	10.0	2.6	6.9	11.4			
II[b]	β-D-*arabino*	3.8	10.3	3.2	~1.0	2.0	13.5			
III	α-D-*lyxo*	1.8	3.2	10.2	5.3	9.5	11.5			
IV[b]	β-D-*ribo*	0.6[c]	3.7	3.7	1.2	1.8	12.0			
V	α-D-*gluco*	3.9	10.0	9.5		9.5		~4.0	~6.0	~12.0
VI	α-D-*galacto*	3.5	10.0	3.1		~3		~0	2.7	~12
VII	α-D-*manno*	1.6	3.0	10.0		9.4		5.0	5.0	12.0
				Acetylated 2-Amino-2-deoxyaldopyranosyl Halides						
VIII[d]	α-D-*gluco*	3.5	8.5	9.5		~9.5				~13.0
IX[e]	α-D-*gluco*	3.5	~9.0	~9.0						
X[f]	α-D-*gluco*	3.5	9.0	~10.0		~10.0				~13.5
				Acetylated Aldopyranoses						
XI	α-D-*lyxo*	3.0	~3.0	9.0	4.1	7.8	11.2			
XII	β-D-*manno*	1.1	3.0	9.5		9.0		5.0	2.4	12.0

[a] By direct measurement from spectra. [b] The $J_{4,5e}$ and $J_{4,5a}$ assignments are not unambiguously differentiated. [c] Width at half-height, 3.0 c.p.s. [d] *N*-Acetyl 1-chloride. [e] Hydrobromide 1-bromide. [f] *N*-(2,4-Dinitrophenyl) 1-bromide.

bromide,[30] which has H-1 and H-2 protons in the *trans*-diaxial arrangement, shows the H-1 signal at τ 3.52 with a large splitting, $J_{1,2}$ = 9.5 c.p.s. A large $J_{1,2}$ coupling constant has also been reported[19] for the H-1 signal in a 40-Mc.p.s. study of tetra-*O*-acetyl-β-D-glucopyranosyl chloride.

Further work in this laboratory is concerned with other hexose configurations and with anomeric equilibria in the poly-*O*-acetylglycosyl halides.

Experimental Section

N.m.r. Measurements.—Spectra were obtained with a Varian A-60 spectrometer. Unless otherwise stated, the spectra were determined at ambient instrument temperature, approximately 30°. The freshly prepared compounds were examined as 10–20% solutions in deuteriochloroform, with tetramethylsilane (τ 10.00) as the internal standard. Peak positions were read directly from precalibrated chart paper; calibration was checked against the chemical-shift difference (436 c.p.s.) between chloroform and tetramethylsilane, and also in some cases by the side-band technique. Coupling constants were measured as direct peak spacings and are considered accurate to ±0.5 c.p.s.; in many cases expanded-scale spectra were also used and give *J* values of greater accuracy than this. Low-temperature spectra were determined with the use of a Varian V-6040 variable temperature probe.

Chemical shift data for methine and methylene proton signals are given in Table I, first-order coupling constants are given in Table II, and chemical shift data for acetyl methyl signals are given in Table III. Additional n.m.r. data are recorded below for compounds VIII–X.

Poly-*O*-acetylglycosyl Bromides.—The appropriate aldoses were acetylated and then converted into the 1-bromides by standard methods. The general procedure of Bárczai-Martos and Kőrösy[31] was used to prepare the following: tri-*O*-acetyl-α-D-xylopyranosyl bromide (I), m.p. 100–102° (lit.[32] m.p. 101–102°); tri-*O*-acetyl-β-D-arabinopyranosyl bromide (II), m.p. 138–140° (lit.[33] m.p. 139°); tetra-*O*-acetyl-α-D-glucopyranosyl bromide (V), m.p. 87–89° (lit.[34] m.p. 88–89°); and tetra-*O*-

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TABLE III

CHEMICAL SHIFTS OF ACETYL METHYL PROTONS

Compd.	Configuration	Chemical shifts, τ (integral, protons) — Axial OAc	Equatorial and primary (OAc and NHAc)
Acetylated Aldopyranosyl Bromides			
I	α-D-*xylo*		7.89 (3), 7.92 (6)
II	β-D-*arabino*	7.86 (3)	7.91 (3), 7.98 (3)
III	α-D-*lyxo*	7.83 (3)	7.90 (3), 7.95 (3)
IV	β-D-*ribo*	7.85 (6)	7.98 (3)
V[a]	α-D-*gluco*		7.91 (6), 7.97 (3), 7.99 (3)
VI	α-D-*galacto*	7.86 (3)	7.91 (3), 7.97 (3), 8.01 (3)
VII	α-D-*manno*	7.83 (3)	7.91 (3), 7.92 (3), 8.00 (3)
Acetylated 2-Amino-2-deoxyaldopyranosyl Halides			
VIII[b]	α-D-*gluco*		7.92 (3), 7.96 (6), 7.99 (3)
IX[c]	α-D-*gluco*		7.77 (3), 7.91 (3), 7.94 (3)
X[d]	α-D-*gluco*		7.89 (3), 7.93 (3), 8.15 (3)
Acetylated Aldopyranoses			
XI	α-D-*lyxo*	7.87 (3), 7.90 (3)	7.95 (3), 7.98 (3)
XII	β-D-*manno*	7.80 (3)	7.90 (6), 7.95 (3), 8.00 (3)

[a] Data supersede values given in ref. 2b. [b] *N*-Acetyl 1-chloride. [c] Hydrobromide 1-bromide. [d] *N*-(2,4-Dinitrophenyl) 1-bromide.

acetyl-α-D-galactopyranosyl bromide (VI), m.p. 84–86° (lit.[35] m.p. 84–85°). Crystalline 1,2,3,4-tetra-*O*-acetyl-β-D-ribopyranose was converted by the method of Levene and Tipson[36] into tri-*O*-acetyl-β-D-ribopyranosyl bromide (IV), m.p. 94° (lit.[36] m.p. 96°). Crystalline 1,2,3,4-tetra-*O*-acetyl-α-D-lyxopyranose (XI) was converted by the method of Levene and Wolfrom[16] into sirupy tri-*O*-acetyl-α-D-lyxopyranosyl bromide (III), $[\alpha]^{28}D$ +95° (*c* 2, chloroform); the solution of XI in hydrogen bromide–acetic acid was kept for 1 hr. at 25° rather than the 20 min. specified by Levene and Wolfrom. Crystalline 1,2,3,4,6-penta-*O*-acetyl-β-D-mannopyranose (XII), m.p. 113–114°, was converted by the method of Levene and Tipson[37] into tetra-*O*-acetyl-α-D-mannopyranosyl bromide (VII), sirup, $[\alpha]^{21}D$ +125° (*c* 0.7, chloroform) [lit.[37] $[\alpha]D$ +123° (chloroform)].

(35) H. Ohle, W. Marecek, and W. Bourjau, *Ber.*, **62**, 833 (1929).
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2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl Chloride[38] **(VIII).**—This compound was prepared directly[39] from 2-acetamido-2-deoxy-D-glucose and had m.p. 125–127° (lit.[39] m.p. 127–128°). The n.m.r. spectrum showed, in addition to the signals listed in Tables I–III, a 1-proton doublet at τ 3.28 (*J* = 9.5 c.p.s., NH proton). This signal disappeared, without observed change in the rest of the spectrum except near τ 5.5 (H-2), when the prepared sample (in $CDCl_3$) was shaken with 0.05 ml. of deuterium oxide for 40 min. at room temperature.

3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl Bromide Hydrobromide[40] **(IX).**—This compound, prepared by an adaptation[41] of the original[40] procedure, had m.p. 149° (lit.[40] m.p. 149–150°). In addition to the data listed in Tables I–III, the n.m.r. spectrum showed a broad 3-proton multiplet at τ 1.38 ($-NH_3^+$).

3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl Bromide[42] **(X).**—This compound, prepared by the procedure of Horton and Wolfrom,[43] had m.p. 160° (lit.[42] m.p. 160–162°). In addition to the data listed in Tables I–III, the n.m.r. spectrum showed the following signals due to the 2 substituent[8]: τ 2.85 (1-proton doublet, *J* = 9.3 c.p.s., NH), 1.71 (1-proton quartet, $J_{5',6'}$ = 9.0 c.p.s., $J_{3',5'}$ = 3.0 c.p.s., H-5′), 1.23 (1-proton doublet, $J_{5',6'}$ = 9.0 c.p.s., H-6′), and 0.90 (1-proton doublet, $J_{3',5'}$ = 3.0 c.p.s., H-3′). The τ 2.85 signal did not undergo deuterium exchange under the conditions used for compound VIII, even after 12 hr.

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Amino Derivatives of Starches. Derivatives of 3,6-Diamino-3,6-dideoxy-D-altrose[1,2]

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Hydrazinolysis of methyl 2,6-di-*O*-(methylsulfonyl)-α-D-glucopyranoside (I), followed by reduction, gives methyl 3,6-diamino-3,6-dideoxy-α-D-altropyranoside, isolable in high yield as the *N,N′*-diacetyl (IV) or *N,N′*-(2,4-dinitrophenyl) (III) derivatives. The structure and stereochemistry of the product were proved by a sequence of degradation reactions and by comparison of the products with derivatives of known α-amino acids. 3,6-Diacetamido-3,6-dideoxy-D-altrose was prepared by way of 3,6-diacetamido-3,6-dideoxy-D-altrose diethyl dithioacetal (XIII).

A program in this laboratory is concerned with the synthesis and structural characterization of aminated polysaccharides derived from starches. An aminated amylose has been prepared[3] from a di-*O*-*p*-tolylsulfonyl derivative of a slightly derivatized amylose, by hydrazinolysis and reduction. Possible reactions of a 2,6-disulfonate ester of amylose, when treated with hydrazine or azide ion and subsequently reduced, have been discussed in the preceding paper in this series. Direct displacement of the sulfonate ester groups would lead to a 2,6-diamino-2,6-dideoxy-D-mannose residue, although more probable routes in the hydrazinolysis reaction would involve either 2,3-epoxide formation with subsequent nitrogen attack at C-3, or 3,6-anhydro ring formation, with or without further displacement at C-2. We have conducted studies on the amination of simple systems to provide models for the reaction in the polysaccharide system and to furnish reference compounds for fragmentation studies on the aminated polysaccharides. 2,6-Diamino-2,6-dideoxy-D-mannose has already been synthesized[4] as such a

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